Defense and Veterans Brain Injury Center "Clinical Updates in Brain Injury
Science Today [CUBIST]" Podcast
"Acute elevation of serum inflammatory markers predicts symptom recovery
after concussion"
TRT: 10:58 min
Host: Ms. Betsy Myhre

_____

[music]

[music]

Myhre: Hi. Welcome to Clinical Updates in Brain Injury Science Today, or "CUBIST," a podcast for health care providers about current research on traumatic brain injury, also known as TBI. This program is produced by the Defense and Veterans Brain Injury Center, otherwise known as DVBIC. I'm your host today, Betsy Myhre. I'm a nurse practitioner here at DVBIC.

This program is produced by the Defense and Veterans Brain Injury Center, otherwise known as DVBIC. I'm your host today, Betsy Myhre. I'm a nurse practitioner in the Clinical Practice and Clinical Recommendations group here at DVBIC.

In today's episode, I'll be talking with Dr. Donald Marion. Dr. Marion is a neurosurgeon at DVBIC. Don and I will discuss a study entitled: Acute elevation of serum inflammatory markers predicts symptom recovery after concussion, by Morgan Nitta and colleagues, and published in Neurology, July 2019.

Myhre: Hi Don, how are you?

Marion: Hi Betsy, good morning

Myhre: Before we discuss this particular research study, can you explain what are biomarkers and some of the different types of biomarkers being studied for TBI?

Marion: Sure, Betsy, that's a great question. So biomarkers are clinical tests that can be used in a variety of ways that can be used for a diagnosis to confirm the presence of a disease that can be used from monitoring to measure serially for assessing a status of a disease that can be used to measure the response of treatment to show that a biological response has occurred. They can be predictive or they can even be prognostic most of the biomarkers that are commonly used for TBI, our protein biomarkers that we obtained from body fluids primarily from blood but they can also be from urine saliva or cerebral spinal fluid. In addition, radiological biomarkers such as CT scans, MRIs, or functional MRI are commonly used for this particular study. And I think for most TBI studies present serum biomarkers or user biomarkers from the blood and basically, that's either two types of these serum biomarker proteins. But in one class of these proteins are structural biomarkers that are intended to tell you something about whether or not there's been damage to the brain in the second class or immunologic biomarkers that are intended to tell you whether or not to spend an inflammatory response that may come either from the periphery or may come directly from the brain.

Myhre: Thanks Don, that provides great context for this research study we're discussing. What were the key findings of this study?

Marion: Betsy, in this study of 84 high school and collegiate football players, serum levels of two inflammatory biomarkers – IL-6, and IL-1 receptor antagonist – significantly discriminated concussed from control athletes at six hours after the concussion. In addition, IL-6 levels at six hours after the concussion were significantly associated with the duration of symptoms that is nearly 50% of concussed athletes with elevated IL-6 levels at six hours, and 44% of athletes with elevated IL-1RA levels at six hours, still were symptomatic at eight days after their concussion. Higher IL-6 levels, though not IL-1RA levels, were associated with slower recovery rates. Of note, none of the concussed athletes had loss of consciousness associated with their TBI.

Myhre: So Don, is that unusual that a study would be conducted on concussed athletes where none of them had a loss of consciousness (LOC)?

Marion: Yeah, I think it is Betsy, and I'm glad you raised that point, I will mention that again in the limitations of the study. But certainly most of know, and certainly most all athletic trainers know that concussion can be associated with at least a brief loss of consciousness.

Myhre: Thanks. How was the study done?

Marion: The subjects of this study were a subset of high school and collegiate football players from southeastern Wisconsin enrolled in a larger prospective study of Sports Related Concussion (SRC) from 2015-2016. Of the 857 athletes enrolled during that time, 90 had a concussion. Forty nine of those athletes were excluded because their concussion was associated with LOC, they had preexisting Adult-Deficit Hyperactivity Disorder (ADHD) or migraines, they had structural findings on MRI, or for other consent or contraindication issues, leaving 41 in the SRC group. After each concussed subject was enrolled, individually matched controls for each injured athlete were identified based on level of play (i.e., college or high school), institution, team, age, estimated intellectual functioning, and multiple other factors. And I think that's kind of an interesting aspect of this study that it was a very personalized matching of controls that they did. A panel of inflammatory biomarkers (IL-6, IL-1β, IL-10, tumor necrosis factor (TNF), C-Reactive Protein (CRP), interferon-γ (IFN-γ) and IL-1 receptor antagonist (IL-1RA)) were assessed from blood draws obtained at pre-season or at baseline, then following concussion at six hours after the concussion, and again at two days, eight days, 15 days and 45 days after the concussion the blood draws were repeated. Post-concussion symptoms were assessed using the symptom scale of The Sport Concussion Assessment Tool, 3rd edition (SCAT3) which was obtained at those same time-points.

Myhre: Why were those inflammatory markers chosen?

Marion: The inflammatory markers were selected, Betsy, were based on previous Traumatic Brain Injury (TBI) studies that found that the inflammatory effects of moderate to severe TBI can best be monitored in the peripheral blood by measuring the inflammatory ILs which are IL-6, IL-1β, IL-10, as well as TNF, C-reactive protein (CRP), and interferon-γ (IFN-γ). In addition, these investigators chose to look at IL-1 receptor antagonist (IL-1RA) levels which was included as a surrogate for IL-1β activity because typically IL-1β levels are pretty low in serum are difficult to detect. It is emphasized that most previous studies were in patients with severe TBI, and the acute inflammatory response following mild TBI (mTBI), or concussion in humans has really not been well-documented.

Myhre: Don, what are the limitations of this study?

Marion: So there actually are several, and some I think are fairly important. First, it is unclear if the origin of IL-6 and IL-1RA are from the brain or the periphery – they can be produced in both places, it is well known that brain injury can cause changes in the peripheral immune function. Second, none of the concussed subjects had LOC so we do not know

what the biomarker profile was like for that subset of concussed football players. Third, since this study was limited to high school and collegiate football players, no females were included. In pre-clinical studies, Donald Stein in Atlanta and others have shown that progesterone suppresses synthesis of TNF-α, IL-1, and IL-6 at both the central and systemic levels, thereby limiting inflammation, microglial activation, and further neuronal injury. So there's reason to believe that the female sex hormone would have an impact immunological proteins and it would be inappropriate to make any assumptions about female athletes based on the results of this study. And finally Betsy, all subjects were asymptomatic at the 15 and 45 day time points so no conclusions can be made about the ability for the six hour biomarker levels to predict long term, greater than eight days post-concussion symptoms.

Myhre: What are the key take-a-ways from this study?

Marion: I think that circulating levels of IL-6 and IL-1RA are increased in the early acute phase following SRC in high school and college football athletes, and IL-6 levels can predict the duration of symptoms   reported by athletes with concussion. These markers may have promise as diagnostic markers of SRC as well as prognostic markers for recovery after SRC. Moreover, these findings highlight the IL-6 and IL-1 pathways as possible targets for treatment of SRC.

In my view, this study also raises two intriguing questions Betsy? First, should sports medicine providers be routinely ordering a blood test for IL-6/IL-1RA following a concussion? And at what time point? And second is, what is the relationship of elevated IL-6/IL-1RA levels to microimaging studies such as Diffuser Tensor Imaging, and to long term behavioral and cognitive problems?

Myhre: Thanks Don. You know I think that this study is a great study that somebody could take and elaborate on. I mean certainly I would love to see this study be done on collegiate female athletes and really look at that. I wonder if they need to expand the study for a larger population.

Marion: Sure, I think most would agree that 41 is a modest amount of subjects.

Myhre: Thank you Don for your insights. That's all we have time for today. We hope you enjoyed this quick literature update.

You can stay up-to-date on future episodes by subscribing to "CUBIST" on iTunes, Stitcher, or wherever you listen to podcasts, where you can also find links to the articles we discuss and other relevant resources.

[music]

"CUBIST" is produced and edited by Vincent White and was hosted today by me, Betsy Myhre. It is a product of the Defense and Veterans Brain Injury Center, led by Division Chief Captain Scott Pyne, Medical Corps, United States Navy.

Thank you for listening to this episode. Next time, we will discuss TBI research getting attention in the mainstream press.

[music]